Variability and randomness in stationary neuronal activity

Lubomir Kostal, Petr Lánský

Institute of Physiology, Academy of Sciences of Czech Republic, Videnska 1083, 142 20 Prague 4, Czech Republic

Address for correspondence:

Lubomir Kostal

Institute of Physiology, Academy of Sciences of Czech Republic,

Videnska 1083,

142 20 Prague 4,

Czech Republic

tel: +420 2 4106 2276,

fax: +420 2 4106 2488,

e-mail: kostal@biomed.cas.cz

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Abstract

The patterns of neuronal activity can be different even if the mean firing rate is fixed. Investigating the variability of the firing may not be sufficient and we suggest to take into account the notion of randomness. The randomness is related to the entropy of the firing, which is bounded from above by the entropy of the Poisson process (given the mean interspike interval). Thus, we propose the Kullback-Leibler distance with respect to the Poisson process as a measure of randomness in a stationary neuronal activity. Under the condition of equal mean values the KL distance does not depend on the time scale and therefore can be compared to the coefficient of variation employed to measure the variability. Furthermore, this measure can be extended to account for correlated neuronal firing. Finally, we analyze the variability and randomness for three common ISI distributions in detail: gamma, lognormal and inverse Gaussian.

Keywords: variability, randomness, entropy, Kullback-Leibler, coefficient of variation

1 Introduction

The discharge activity of neurons is composed of the series of events called action potentials or spikes. It is generally accepted that the information in neuronal systems is transferred by the time series of spikes – the spike trains. There are two main hypotheses that attempt to classify possible ways in which the spike trains may

carry information: the frequency (rate) codes and the temporal codes (Gerstner and Kistler, 2002; Theunissen and Miller, 1995). The classical results in early neuroscience (Adrian, 1928) show that the number of spikes per a time period (the firing rate) is related to the stimulus intensity, i.e., the firing rate increases with increasing stimulus intensity. The idea of temporal spike coding (Perkel and Bullock, 1968; Theunissen and Miller, 1995), on the other hand, employs the timing of the spikes or the particular ordering of interspike intervals. Whereas frequency code has quite specific meaning, the temporal code denotes all alternatives not classified as the former one. Therefore, the temporal coding involves on one hand precise patterns of spikes and on the other hand, for example, variability differences in the firing. Searching and comparing variability of different spike trains is a traditional tool in neuroscience studies. It holds for experimental as well as model spike trains and the most common way is by calculating the coefficient of variation (C_V) of interspike intervals (ISI).

The frequency codes in single neurons may carry information about both dynamic and stationary stimuli, see overview in Theunissen and Miller (1995). If the the neuronal firing is stationary then the mean spike frequency (the inverse of the mean ISI, Lánský et al. (2004)) carries the information from the frequency coding hypothesis point of view. The temporal coding, on the other hand, has been shown to occur almost exclusively under steady-state stimulus conditions (Fuller and Looft, 1984; Middlebrooks et al., 1994). Therefore to classify the spike trains solely from the temporal coding scheme point of view, one needs to describe differences between various stationary firing regimes with equal mean ISI.

The aim of this paper is to characterize the stationary neuronal firing. The method is based on a measure of randomness and we compare it with a measure of variability. The examples are restricted on the renewal spiking activity despite the fact that a general theory is available. The reason is that for the renewal model

analytical results can be obtained, while there are no descriptions of correlated neuronal activity both realistic and mathematically suitable for our purpose.

2 Methods

2.1 Variability

Neuronal firing under stable conditions is often described as a renewal process of ISIs. In such a case the ISIs are mutually independent realizations of a positive random variable T and are fully characterized by the probability density function $f(t)$, where $f(t)\,dt = \mathrm{Prob}(T \in [t, t+dt))$ (Cox and Lewis, 1966). The renewal character of the ISIs implies stationarity of the neuronal activity. Often, though the neuronal firing is stationary, there is a dependency structure among the observed ISIs (Chacron et al., 2001; Longtin and Racicot, 1996). The dependence may arise due to the incomplete resetting of the membrane potential after the spike is emitted, which is experimentally observed especially in the distal parts of the neuron (Abeles, 1982). The other source of dependency may be a time structure in the input of the neuron. The successive ISIs $\{T_i\}$ are then statistically dependent, but due to the stationarity the expected value $E(T) = E(T_i)$ exists. The activity is fully described by the joint probability density function $f(t_1, t_2, \dots)$, see, e.g., Cox and Lewis (1966) for details.

The patterns of stationary neuronal activity may be strikingly different even if the mean firing rate, or equivalently the mean ISI, is fixed. The variability is probably the first issue to consider. It is often measured by employing the variance, $Var(T)$, or the coefficient of variation, C_V, which relates variance to mean value, $C_V = \sqrt{Var(T)}/E(T)$. The main advantage of C_V over $Var(T)$ – and the reason why it is used in data analysis – is that C_V does not depend on the 'scaling',

$C_V(aT) = C_V(T)$. In other words, C_V is dimensionless and can be used to compare variability of spike trains with different mean ISI. For the Poisson process holds $C_V = 1$ independently of $E(T)$. The differences in variability for several firing regimes are shown in Fig. 1A–C.

Even if the mean firing rate and variability of the neuronal firing are the same, the resulting spike trains may still have very different properties, compare Fig. 1A, D and E. The spike train in Fig. 1D is realized by the renewal process with Bernoulli distribution of ISIs and parameters chosen so that $C_V = 1$ just as in the case of the Poisson process in Fig. 1A. In other words, though Poisson process implies $C_V = 1$ the reverse implication does not hold. The example in Fig. 1E shows a spike train with $C_V = 1$ again, but with properties significantly different from that of the Poisson firing (though the ISI densities of Fig. 1A and Fig. 1E are the same). The successive ISIs in Fig. 1E are not independent and the first-order serial correlation is $\varrho = 0.86$. Thus, such a neuronal firing is not described by the renewal process. We may conclude by comparing spiking activities in Fig. 1A, D and E, that even though the variability is the same, the randomness of the firing can be different. We take this fact as an indication that the classification of stationary firing may be based also on different qualities than variability. In the following text we will precise the notion of randomness (or uncertainty) in neuronal activity.

Next we introduce three "standard" renewal-process models of neuronal firing. These are gamma, inverse Gaussian and lognormal ISI distributions and we analyze their properties with respect to variability and randomness. The three mentioned distributions are fully determined by two parameters. We choose C_V as a paremeter in order to employ variability directly. The C_V ranges from zero to infinity for all three mentioned models. We let the remaining parameter be the mean ISI, $\mu = E(T)$, which makes comparing distributions with equal $E(T)$ easier.

Gamma distribution is one of the most frequent statistical descriptors of ISIs

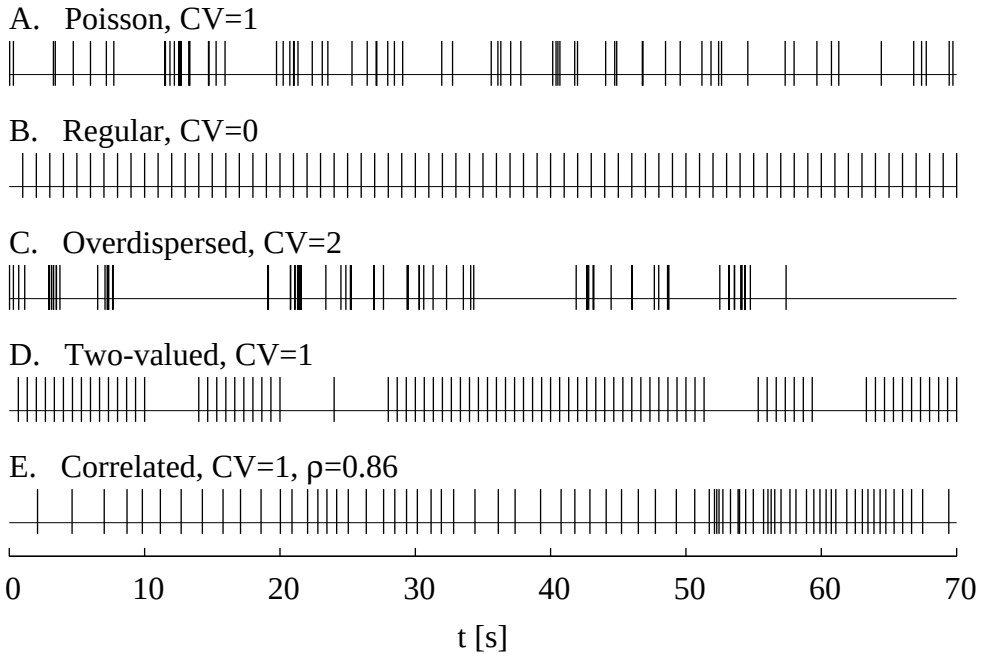

Fig. 1: Simulated spike trains illustrating the variability in stationary neuronal firing with $E(T) = 1\,\mathrm{s}$ and different C_V. (A) Poisson process, $C_V = 1$. (B) regular firing, $C_V = 0$. (C) bursting neuronal activity (overdispersed firing), $C_V > 1$. (D) renewal process with Bernoulli distribution of ISIs, $C_V = 1$. (E) activity 'derived' from the Poisson process (ISI densities are the same, thus $C_V = 1$). The ISIs are ordered so that the serial correlation ϱ between two successive ISIs is $\varrho = 0.86$.

(Hentall, 2000; Levine, 1991; McKeegan, 2002; Mandl, 1992; Reeke and Coop, 2004). Its probability density function is

$$f(t) = \left(\frac{1}{C_V^2 \mu}\right)^{1/C_V^2} \Gamma(1/C_V^2)\, t^{1/C_V^2 - 1} \exp\left(-\frac{t}{C_V^2 \mu}\right), \tag{1}$$

where $\Gamma(z) = \int_0^\infty t^{z-1} \exp(-t)\, dt$ is the gamma function. For $C_V = 1$ it becomes exponential.

The inverse Gaussian distribution (Chhikhara and Folks, 1989) is often used

to describe neural activity (Iynegar and Liao, 1997) and fitted to experimentally observed ISIs (Berger et al., 1990; Berger and Pribram, 1992; Gerstein and Mandelbrot, 1964; Levine, 1991). This distribution results from the Wiener process with positive drift (the depolarization has a linear trend to the threshold) and describes the spiking activity of non-leaky integrate-and-fire stochastic neuronal model (Ricciardi and Lansky, 2003). The probability density of the inverse Gaussian distribution can be expressed as

$$f(t) = \sqrt{\frac{\mu}{2\pi C_V^2 t^3}} \exp\left[-\frac{1}{2C_V^2\mu}\frac{(t-\mu)^2}{t}\right]. \tag{2}$$

The lognormal distribution of ISI, with some exceptions (Bershadskii et al., 2001), is rarely presented as a result of a neuronal model. However, it represents quite a common descriptor in ISI data analysis (Levine, 1991), e.g., a mixture of two lognormal distributions has been used recently (Bhumbra et al., 2004). It is given by the probability density function

$$f(t) = \frac{1}{t\sqrt{2\pi \ln(1+C_V^2)}} \exp\left\{-\frac{1}{8}\frac{\left[\ln(1+C_V^2) + 2\ln(t/\mu)\right]^2}{\ln(1+C_V^2)}\right\}. \tag{3}$$

Neither the inverse Gaussian nor the lognormal distribution is exponential for $C_V = 1$.

2.2 Randomness

The randomness of the renewal process with probability density function $f(t)$ can be judged by using the hazard rate $r(t)$,

$$r(t) = \frac{f(t)}{1 - F(t)}, \tag{4}$$

where $F(t)$ is the cumulative distribution function $F(t) = \int_0^t f(z)\,dz$. The hazard rate determines the probability of spike occurrence in interval $[t, t + dt)$ under the condition that there was no firing in $[0, t)$. The most random firing is such that with elapsed time from the previous spike the probability of the next one does not change. It is well known that this holds for the renewal process with exponential distribution of ISIs. We denote the exponential probability density function as $g(t)$,

$$g(t) = \frac{1}{\mu} e^{-t/\mu}, \tag{5}$$

retaining the condition $E(T) = \mu$. The hazard rate for density (5) is then $r(t) = 1/\mu$.

Function $r(t)$ reflects the randomness of the renewal process but if we wish to relate it to the single value of C_V, we need to find a single-valued counterpart. The question how to measure the randomness of any renewal process with probability density $f(t)$ is answered by the concept of (differential) entropy, $h(f)$,

$$h(f) = -\int_0^\infty f(t) \ln f(t)\,dt. \tag{6}$$

The entropy $h(f)$ does not share the same properties and intuitive interpretation as the entropy H of a discrete probability mass function (Cover and Thomas, 1991). Namely, it can be negative and its value changes with a coordinate transform. Nevertheless, the most 'random' distribution is still the one that maximizes $h(f)$. The Poisson process thus represents the 'zero point' on the scale measuring the randomness of neuronal firing and we will relate it to any other stationary neuronal activity. It is not reasonable to choose regular spiking as the 'zero point' because the entropy h of the Dirac δ-distribution is $h = -\infty$ (Cover and Thomas, 1991). A measure $D(f, g)$ relating a renewal process with ISI probability density $f(t)$ to the Poisson process with the same mean value $\mu = E(T)$ is realized by the difference of

the respective entropies,

$$D(f, g) = h(g) - h(f). \tag{7}$$

From equations (5) and (6) follows that $h(g) = 1 + \ln \mu$ and then

$$D(f, g) = 1 + \ln \mu - h(f). \tag{8}$$

The proposed measure of randomnes thus gives increasing values with decreasing randomness.

Formula (7) is related to the more general notion of Kullback-Leibler (KL) distance (relative entropy) of two probability density functions defined as

$$\mathrm{KL}(f, g) = \int_0^\infty f(t) \ln \frac{f(t)}{g(t)}\, dt, \tag{9}$$

(Cover and Thomas, 1991). Calculation shows immediately that if the mean values of $f(t)$ and $g(t)$ in formula (9) are the same and $g(t)$ is exponential then

$$\mathrm{KL}(f, g) = D(f, g). \tag{10}$$

Thus, the KL distance of a probability density function $f(t)$ from the exponential density under the condition of equal mean values can be used as a measure of randomness of a renewal neuronal activity.

Formula (10) can be extended to include any non-renewal stationary neuronal activity (see example in Fig. 1E). In such a case the activity is fully described by the joint probability density function $f(t_1, t_2, \dots)$. The Kullback-Leibler distance

per ISI then takes form

$$\mathrm{KL}(f,g) = \lim_{n\to\infty} \frac{1}{n} \int_0^\infty \cdots \int_0^\infty f(t_1,\ldots,t_n) \ln \frac{f(t_1,\ldots,t_n)}{g(t_1,\ldots,t_n)}\, dt_1 \ldots dt_n, \qquad (11)$$

see Cover and Thomas (1991) for details. Formula (11) corresponds to the original definition (9) for the renewal process. Conditioning reduces entropy (Cover and Thomas, 1991) and thus the Poisson process maximizes entropy even in the generalized case. Letting $g(t_1,\ldots,t_n) = (1/\mu)^n \exp\left(-\sum_{i=1}^n t_i/\mu\right)$ in formula (11) and setting the mean values of $f(t_1,t_2,\ldots)$ and $g(t_1,t_2,\ldots)$ equal to $E(T)$ (this is possible because both activities are stationary) yields

$$\mathrm{KL}(f,g) = h(g) - \bar{h}(f), \qquad (12)$$

where

$$\bar{h}(f) = -\lim_{n\to\infty} \frac{1}{n} \int_0^\infty \cdots \int_0^\infty f(t_1,\ldots,t_n) \ln f(t_1,\ldots,t_n)\, dt_1 \ldots dt_n. \qquad (13)$$

Note that by taking the difference of two entropies in formula (7) instead of employing $h(f)$ directly, and by relating the result to the concept of the KL distance, several important issues are solved and some new properties emerge:

- $D(f,g)$ does not depend on coordinate transforms because in formula (11) both nominator and denominator are multiplied by the same factors.

- $D(f,g) \geq 0$ with equality if and only if $f(t)$ is exponential because $g(t)$ maximizes the entropy.

- $D(f,g)$ does not depend on $E(T)$ due to the invariance of KL distance to coordinate transforms. The logarithm of a time unit ($\ln E(T)$) "cancels out"

as can be seen from the general formula (11).

3 Results

In this section we illustrate the application of formula (10) on the neuronal firing models given by equations (1)–(3). Using formula (6), the entropy of gamma distribution (1) is

$$h(f) = \frac{1}{C_V^2} + \ln\left(\frac{1}{\mu C_V^2}\right) + \ln\Gamma\left(\frac{1}{C_V^2}\right) + \left(1 - \frac{1}{C_V^2}\right)\Psi\left(\frac{1}{C_V^2}\right), \tag{14}$$

where $\Psi(z) = \frac{d}{dz}\ln\Gamma(z)$ is the digamma function. Combining equations (8) and (14) we find the KL distance of the gamma distribution from the exponential one,

$$\mathrm{KL}(C_V) = \ln\frac{e}{CV^2} - \ln\Gamma\left(1/C_V^2\right) + \frac{\Psi(1/C_V^2) - 1}{C_V^2} - \Psi(1/C_V^2). \tag{15}$$

This result is illustrated in Fig. 2. Note that formula (15) does indeed not depend on $E(T)$ as mentioned before. The density f given by formula (1) is exponential for $C_V = 1$ and therefore $\mathrm{KL}(C_V = 1) = 0$. The KL distance tends to infinity for $C_V \to 0$ and $C_V \to \infty$. We can see from Fig. 2 that $\mathrm{KL}(C_V)$ increases rapidly for $C_V > 1$, especially if compared to the other models presented here. For $C_V < 0.25$ (approximately) the KL distances of gamma, lognormal and inverse Gaussian distributions become the same. The exponentiality of the gamma distribution for $C_V = 1$ and its difference from the Poisson process at $C_V = 2$ is illustrated using the hazard rates and probability density functions in Fig. 3.

The identical approach as in the previous case reveals that the KL distance of the inverse Gaussian distribution (2) from the exponential one is

$$\mathrm{KL}(C_V) = \frac{1}{2}\ln\frac{e}{2\pi C_V^2} + \frac{3\,e^{1/C_V^2}}{\sqrt{2\pi C_V^2}} K_{\frac{1}{2}}^{(1,0)}(1/C_V^2), \tag{16}$$

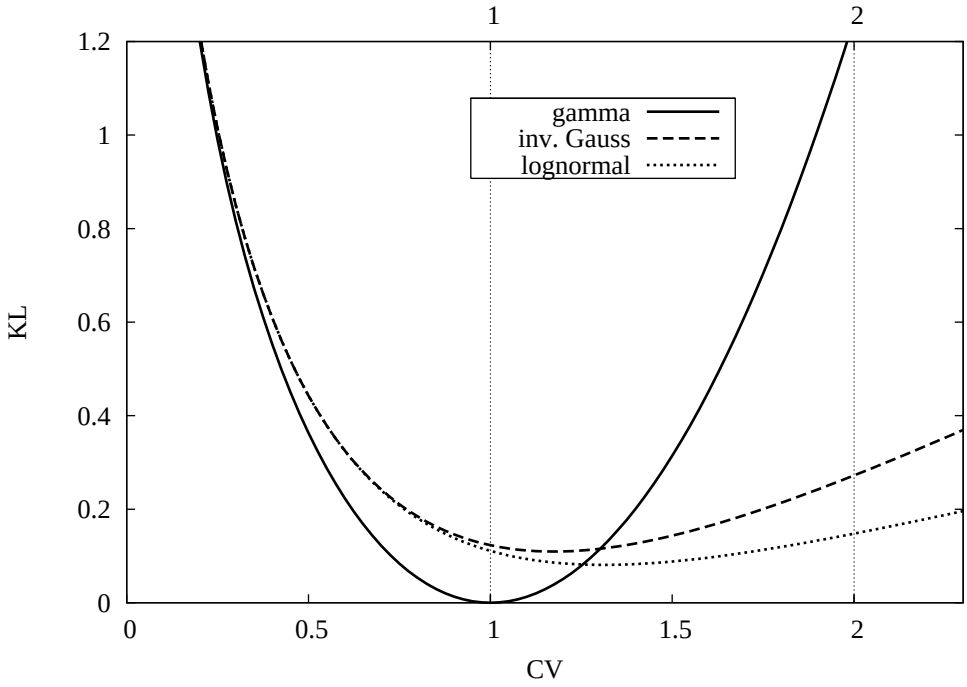

Fig. 2: The Kullback-Leibler (KL) distance as a function of C_V for three models of neuronal activity. The KL distance of the gamma distribution is zero for $C_V = 1$, implying that at this point it becomes exponential. Near $C_V = 1$ the values of KL distances are generally low. The minimum for the lognormal resp. inverse Gaussian distribution is located at $C_V \approx 1.31$, resp. $C_V \approx 1.17$. The distributions never become exponential. For $C_V \to 0$ and for $C_V \to \infty$ the KL distances tend to infinity. For C_V close zero the KL distances are initially the same. In general, low variability implies low randomness in the firing. On the other hand, the KL distances of the lognormal and inverse Gaussian grow very slowly with increasing C_V compared to the gamma distribution. This means that high variability may results in high as well as low randomness.

where $K_\nu^{(1,0)}(z)$ is the derivative of the modified Bessel function of the second kind (Abramowitz and Stegun, 1972), $K_\nu^{(1,0)}(z) = \frac{\partial}{\partial \nu} K_\nu(z)$. The dependence is shown in

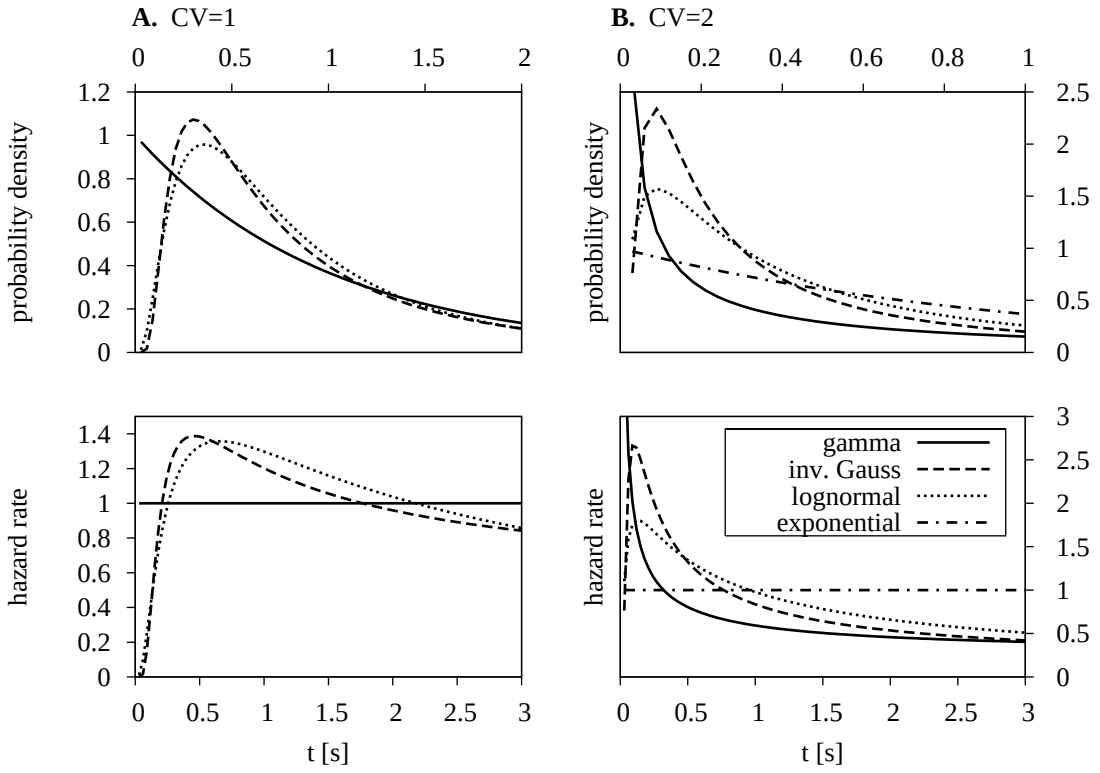

Fig. 3: Comparison of hazard rates and probability densities of the tested models with $E(T) = 1\,\mathrm{s}$ for two values of C_V. (A) $C_V = 1$. The gamma distribution reduces to the exponential one. The hazard rates of inverse Gaussian and lognormal distributions are very similar in shape but none is constant. The lognormal and inverse Gaussian distributions can be hardly distinguished based on the hazard rates or densities and it is reflected in nearly equivalent values of the KL distance, see Fig. 2. (B) $C_V = 2$. The hazard rates are more different. In analogy with the KL distance, the lognormal is 'closest' to the exponential and gamma distribution is the most different. Similar (only less prominent) observation is yielded by comparing the probability density functions.

Fig. 2. Due to the fact that the inverse Gaussian is never exponential, $\mathrm{KL}(C_V) > 0$. The minimum of $\mathrm{KL}(C_V)$ for the inverse Gaussian distribution is located at

$C_V \approx 1.173$. We can see a difference compared to the gamma distribution. It has been already noted that the condition $C_V = 1$ does not imply exponentiality but in this case even the minimal distance is not located at $C_V = 1$, but at $C_V \approx 1.17$.

Finally, the KL distance of lognormal distribution (3) from the exponential one is

$$\mathrm{KL}(C_V) = \frac{1}{2}\left[\ln \frac{C_V^2 + 1}{\ln(C_V^2 + 1)} + \ln \frac{e}{2\pi}\right] \tag{17}$$

and the minimum is at $C_V = \sqrt{e-1} \approx 1.311$. Again, the minimal possible deviation of lognormal distribution from exponential one is not at $C_V = 1$. It is interesting that for $C_V < 1$ (approximately) there is no difference in lognormal and inverse Gaussian distributions from the perspective of the KL distance. The equality in the KL distance, however, does not imply that these distributions are identical.

4 Conclusions

We demonstrated that variability in stationary neuronal firing is not sufficient to describe different firing regimes with equal mean ISI and that the notion of randomness brings an alternate point of view. The Kullback-Leibler (KL) distance was proposed as a measure of randomness with the exponential distribution being chosen as a template, because the exponential distribution is the most random one (maximizes entropy). Under the condition of equal mean values the KL distance resolves the problems of differential entropy and satisfies additional useful properties.

We concentrated mainly on the neuronal firing described by the renewal process and we analyzed three common two-parametric distributions using the proposed method: gamma, lognormal and inverse Gaussian. The following inference can be made on the basis of the KL distance of ISI distributions:

1. The KL distances for all three investigated distributions is U-shaped with low

values distributed around $CV = 1$.

2. While small variability generally implies low randomness, high variability in the firing may result in both low as well as high randomness.

3. The same level of randomness in the firing can be obtained with different values of variability. Therefore the notions of randomness and variability represent different descriptions of the neuronal activity.

4. It is well known that the lognormal and inverse Gaussian distributions never become exponential but in addition their minimal KL distances to this distribution are not located at $C_V = 1$.

5. For C_V increasing from zero (regular spiking) the KL distances of lognormal, inverse Gaussian and gamma distributions are initially the same. Then gamma branches off at $C_V \approx 0.25$ and the lognormal and inverse Gaussian depart at $C_V \approx 1$.

6. For lognormal and inverse Gaussian distributions the KL distance grows very slowly for $C_V > 1$, compared to the gamma distribution and their distances to the exponential distribution are practically the same for $C_V = 1$ as for $C_V < 2$.

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